NEOPLASIA
www.neoplasia.com
Volume 17 Number 2 February 2015 pp. 153–154 153

COMMENTARY

BUB1-bling over with Possibilities

Mary Helen Barcellos-Hoff

Department of Radiation Oncology New York University, School of Medicine, New York, NY

Abstract

In a new report, Nyati et al. identified a previously undetected participant mediating both canonical signaling, i.e., TGF-β receptor kinase mediated, and non-canonical signaling, budding uninhibited by benzimidazole 1 (BUB1).

Neoplasia (2015) 17, 153–154

Despite more than a quarter century and a vast literature, understanding transforming growth factor–β (TGFβ) signaling continues to be a major research enterprise because TGFβ is a central hub in both homeostasis and disease. The TGFβ1 isoform is the founding member of a superfamily that orchestrates cell interactions, regulates phenotype, and acts as a critical switch in many key tissue repair processes. In a new report, Nyati et al. has identified a previously undetected participant mediating both canonical, i.e., TGFβ receptor kinase mediated, and non-canonical signaling [1]. This group conducted a small interfering RNA (siRNA) screen of the human kinome using a live-cell reporter for TGFβ receptor (TGFBR) activity in two cancer lines. The screen successfully identified many proteins with known roles, and the authors chose to characterize budding uninhibited by benzimidazole 1 (BUB1) as a target using a high stringency strategy for selection. BUB1 was validated in six malignant and non-malignant human cell lines from various tissues in which siRNA activity abrogated the activation of SMAD2 and SMAD3 as well as components of the non-canonical signaling cascade (c-JUN, p38 mitogen-activated protein kinase, and AKT). Although BUB1 knockdown in one cell line, A549, also decreased TGFBR type I (TGFBRI), this was not necessary in other cell lines nor did BUB1 siRNA mimic TGFBRI small molecule inhibitor effects, confirming it as an independent mediator of TGFβ signaling.

BUB1 depletion abrogated the formation of the TGFBRI–TGFBR type II (TGFBRII) complex. The authors showed that BUB1 promotes the TGFBRI-TGFBRII complex formation, in which BUB1 interacts with both TGFBRI and TGFBRII, but does not require TGFBR1 kinase activity. However, BUB1 kinase activity is necessary for TGFβ canonical signaling even though BUB1 does not directly phosphorylate TGFBRI or phosphorylate purified SMAD3 *in vitro*. Importantly, BUB1 kinase activity is also important for non-canonical signaling through Akt and p38 mitogen-activated protein kinase. The authors conclude that BUB1 forms a ternary complex with the ligand and both receptors; signaling requires BUB1's Ser/Thr kinase activity, but the actual BUB1 substrate required for TGFβ signaling is as yet unknown.

Thus, BUB1 joins the ongoing delineation of TGFβ signaling in a complex network that controls its actions across cell types, but this new member is particularly intriguing in regards to cancer. The TGFβ switch from tumor suppressor to tumor promoter remains one of the major hallmarks of epithelial cancers, whose normal counterparts are profoundly growth inhibited by femtomolar TGFβ concentrations. BUB1 is a mitotic checkpoint protein that also has a role in regulating kinetochore-microtubule attachments (reviewed in [2]). Notably, its deletion rapidly leads to aneuploidy, which is a relatively underappreciated consequence of TGFβ1 knockout [3,4].

Nyati et al. have uncovered a pathway interaction that has far-reaching implications in understanding the loss of genomic stability in cancer and may have therapeutic applications as well. Intriguingly, there is growing evidence that TGFβ is necessary for genomic stability and pluripotency in stem cells and DNA damage response in differentiated cells. In one study of five human embryonic stem cell lines, BUB1 is among the 1% of genes expressed across all lines in the undifferentiated states, and clustered with previously reported stemness genes responsible for self-renewal and pluripotent differentiation, concurrent with highly expressed TGFβ

Abbreviations: TGFβ, transforming growth factor–β; BUB1, budding uninhibited by benzimidazole 1; TGFBRII, TGFβ receptor type II; TGFBRI, TGFβ receptor type I

Address all correspondence to: Mary Helen Barcellos-Hoff, Department of Radiation Oncology New York University, School of Medicine 566 First Avenue, New York, NY 10016.
E-mail: mhbarcellos-hoff@nyumc.org

Conflict of interest: The author has no conflicts of interest regarding this commentary.
Author contributions: M.H.B.-H.—manuscript writing.

Commentary on "Nyati S, Schinske-Sebolt K, Pitchiaya S, Chekhovskiy K, Chator A, Chaudhry N, Dosch J, Van Dort ME, Varambally S, Kumar-Sinha C, et al. (2014). The Ser/Thr kinase BUB1 and its kinase activity mediates transforming growth factor β signaling. *Sci Signal*, in press".
Received 6 January 2015; Accepted 7 January 2015

1476-5586/15
http://dx.doi.org/10.1016/j.neo.2015.01.002

signaling components, TGFBRI and SMAD2 [5]. Of particular interest is that either BUB1 [6] or TGFβ1 deletion [7] impairs DNA damage recognition and increases sensitivity to ionizing radiation. This is one example of many neoplastic processes in which TGFβ is implicated, and underscores how the addition of BUB1 as a necessary component of TGFβ signaling has the potential to clarify the aspects of TGFβ phenotypes that have long puzzled the community.

References

[1] Nyati S, Schinske-Sebolt K, Pitchiaya S, Chekhovskiy K, Chator A, Chaudhry N, Dosch J, Van Dort ME, Varambally S, and Kumar-Sinha C, et al (2015). The Ser/Thr kinase BUB1 and its kinase activity mediates transforming growth factor β signaling. *Sci Signal* **8**(358), ra1. http://dx.doi.org/10.1126/scisignal.2005379.

[2] Elowe S (2011). Bub1 and BubR1: at the interface between chromosome attachment and the spindle checkpoint. *Mol Cell Biol* **31**, 3085–3093.

[3] Glick AB, Weinberg WC, Wu IH, Quan W, and Yuspa SH (1996). Transforming growth factor β1 suppresses genomic instability independent of a G_1 arrest, *p53*, and *Rb*. *Cancer Res* **56**, 3645–3650.

[4] Maxwell CA, Fleisch MC, Costes SV, Erickson AC, Boissiere A, Gupta R, Ravani SA, Parvin B, and Barcellos-Hoff MH (2008). Targeted and nontargeted effects of ionizing radiation that impact genomic instability. *Cancer Res* **68**, 8304–8311.

[5] Li SS, Liu YH, Tseng CN, Chung TL, Lee TY, and Singh S (2006). Characterization and gene expression profiling of five new human embryonic stem cell lines derived in Taiwan. *Stem Cells Dev* **15**, 532–555.

[6] Yang C, Wang H, Xu Y, Brinkman KL, Ishiyama H, Wong ST, and Xu B (2012). The kinetochore protein Bub1 participates in the DNA damage response. *DNA Repair* **11**, 185–191.

[7] Kirshner J, Jobling MF, Pajares MJ, Ravani SA, Glick A, Lavin M, Koslov S, Shiloh Y, and Barcellos-Hoff MH (2006). Inhibition of TGFβ1 signaling attenuates ATM activity in response to genotoxic stress. *Cancer Res* **66**, 10861–10868.